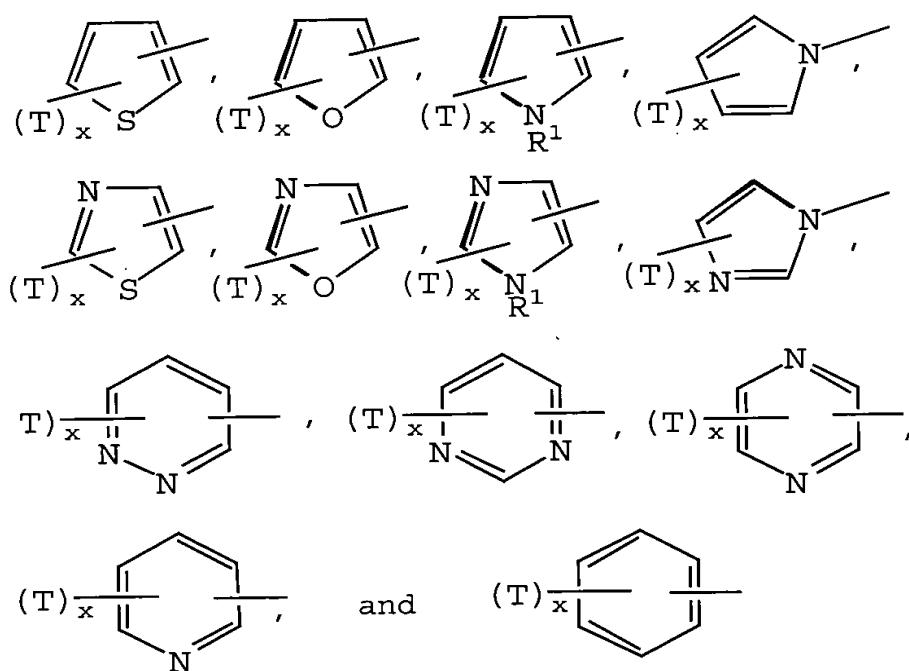


1. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of a compound having matrix metalloprotease inhibitory activity and the generalized formula:



wherein

- (a) $(T)_x A$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



wherein R^1 represents H or alkyl of 1 - 3 carbons; and

each T represents a substituent group, independently selected from the group consisting of:

- * the halogens -F, -Cl, -Br, and -I;
- * alkyl of 1 - 10 carbons;
- * haloalkyl of 1 - 10 carbons;

- * haloalkoxy of 1 - 10 carbons;
- * alkenyl of 2 - 10 carbons;
- * alkynyl of 2 - 10 carbons;
- * -(CH₂)_pQ , wherein

p is 0 or an integer 1 - 4,
- * -alkenyl-Q, wherein

said alkenyl moiety comprises 2 - 4 carbons, and
- * -alkynyl-Q , wherein

said alkynyl moiety comprises 2 - 7 carbons; and

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Q is selected from the group consisting of aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, -CN, -CHO, -NO₂, -CO₂R², -OCOR², -SOR³, -SO₂R³, -CON(R⁴)₂ , -SO₂N(R⁴)₂ , -C(O)R² , -N(R⁴)₂, -N(R²)COR², -N(R²)CO₂R³ , -N(R²)CON(R⁴)₂, -CHN₄, -OR⁴, and -SR⁴;

wherein

R² represents H;
alkyl of 1 - 6 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

R³ represents alkyl of 1 - 4 carbons;
aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

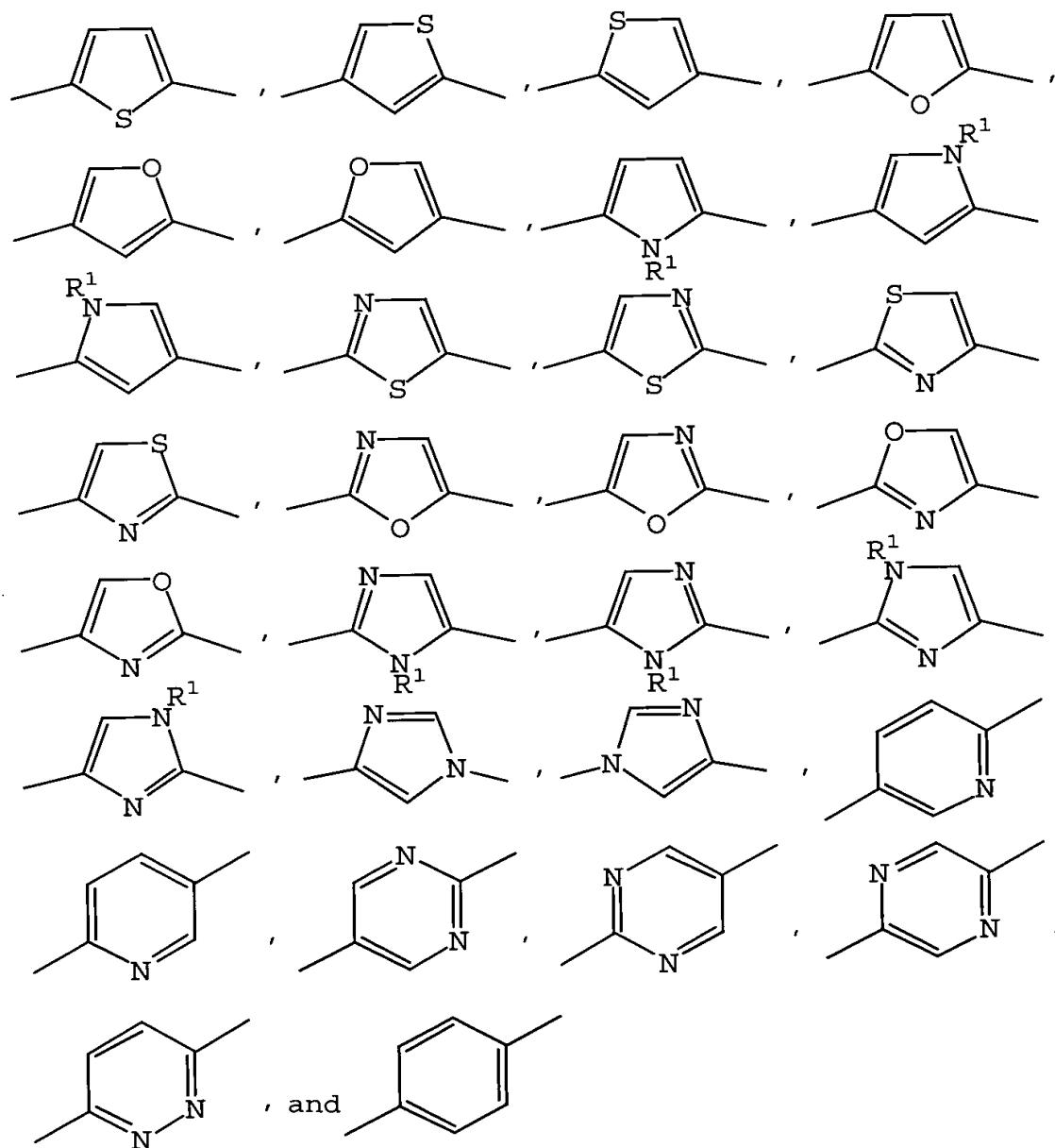
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 R^4 represents H;
alkyl of 1 - 12 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;
alkenyl of 2 - 12 carbons;
alkynyl of 2 - 12 carbons;
 $-(C_qH_{2q}O)_rR^5$ wherein q is 1-3; r is 1 - 3; and R^5 is H provided q is greater than 1, or alkyl of 1 - 4 carbons, or phenyl; alkylenethio terminated with H, alkyl of 1-4 Carbons, or phenyl; alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl;
 $-(CH_2)_sX$ wherein s is 1 - 3 and X is halogen;
 $-C(O)OR^2$; or
 $-C(O)R^2$;

and with the provisos that a) when two R^4 groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part

of Q is separated from any N, O, or S of Q by at least one carbon atom, and

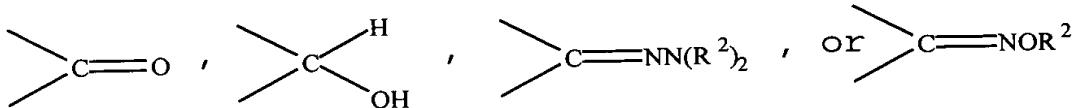
x is 0, 1, or 2;

- (b) B represents a bond or an optionally substituted aromatic or heteroaromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:



wherein R¹ is as defined above;

(c) D represents



in which R² is defined as above and each R² may be the same or different;

(d) E represents a chain of n carbon atoms bearing m substituents R⁶, wherein said R⁶ groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R⁶ are joined, and taken together with the chain atom(s) to which said two R⁶ group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R⁶ is joined to the chain on which said one group R⁶ resides, and taken together with the chain atom(s) to which said R⁶ group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein
n is 2 or 3;
m is an integer of 1 - 3;

each group R⁶ is independently selected from the group consisting of:

- * fluorine;
- * hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent
- * alkyl of 1 - 10 carbons;
- * aryl of 6 - 10 carbons;
- * heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
- * arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

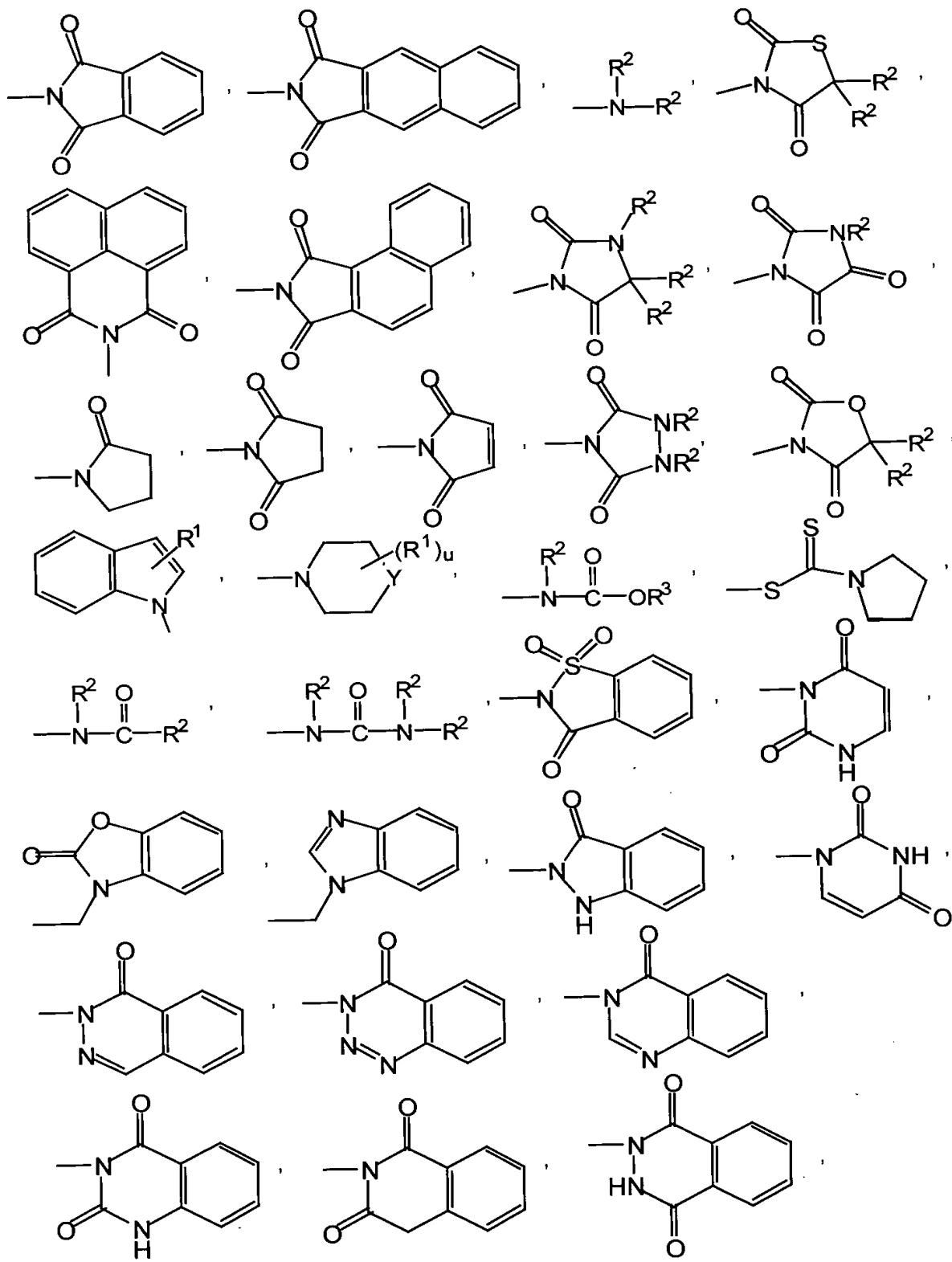
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A

- * heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
- * alkenyl of 2 - 10 carbons;
- * aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;
- * heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;
- * alkynyl of 2 - 10 carbons;
- * aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
- * heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
- * $-(CH_2)_tR^7$ wherein
t is 0 or an integer of 1 - 5; and
 R^7 is selected from the group consisting of

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and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R⁷ group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

Y represents O or S;

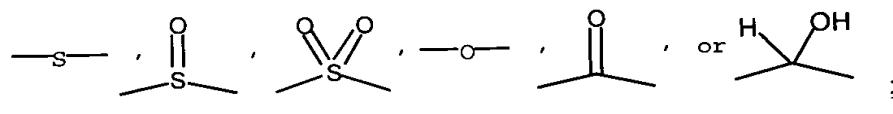
R¹, R², and R³ are as defined above; and

u is 0, 1, or 2; and

* -(CH₂)_vZR⁸ wherein

v is 0 or an integer of 1 to 4; and

Z represents



R⁸ is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

-C(O)R⁹ wherein R⁹ represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R⁸ is -C(O)R⁹, Z is S or O;
- when Z is O, R⁸ may also be -(C_qH_{2q}O)_rR⁵ wherein q, r, and R⁵ are as defined above; and

- * -(CH₂)_wSiR¹⁰₃ wherein
w is an integer of 1 to 3; and
R¹⁰ represents alkyl of 1 to 2 carbons;

and with the proviso that

- aryl or heteroaryl portions of any of said T or R⁶ groups optionally may bear up to two substituents selected from the group consisting of

-(CH₂)_yC(R⁴)(R³)OH, -(CH₂)_yOR⁴, -(CH₂)_ySR⁴, -(CH₂)_yS(O)R⁴,
-(CH₂)_yS(O)₂R⁴, -(CH₂)_ySO₂N(R⁴)₂, -(CH₂)_yN(R⁴)₂, -(CH₂)_yN(R⁴)COR³,
-OC(R⁴)₂O- in which both oxygen atoms are connected to the aryl ring,
-(CH₂)_yCOR⁴, -(CH₂)_yCON(R⁴)₂, -(CH₂)_yCO₂R⁴, -(CH₂)_yOCOR⁴,
-halogen, -CHO, -CF₃, -NO₂, -CN, and -R³, wherein

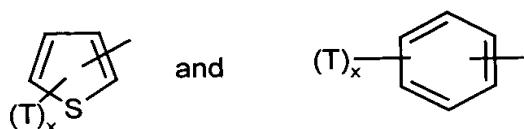
y is 0 - 4; and

R³ and R⁴ are defined as above; and any two R⁴ which are attached to one nitrogen may be joined to form a heterocycle;

and pharmaceutically acceptable salts and prodrugs thereof.

2. (Amended) The method of claim 1, wherein

- (a) (T)_xA represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



wherein

each T represents a substituent group, independently selected from the group consisting of:

- * the halogens -F, -Cl, -Br, and -I;
- * alkyl of 1 - 10 carbons;
- * haloalkyl of 1 - 10 carbons;
- * alkenyl of 2 - 10 carbons;
- * alkynyl of 2 - 10 carbons;
- * $-(CH_2)_pQ$, wherein
 - p is 0 or an integer 1 - 4,
- * -alkenyl-Q, wherein
 - said alkenyl moiety comprises 2 - 4 carbons, and
- * -alkynyl-Q, wherein
 - said alkynyl moiety comprises 2 - 7 carbons; and

A¹

Q is selected from the group consisting of -OR⁴ and -SR⁴;

wherein

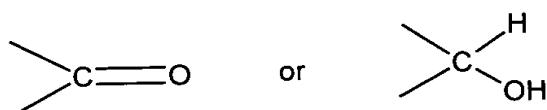
R⁴ represents H;

- alkyl of 1 - 12 carbons;
- aryl of 6 - 10 carbons;
- heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
- arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;
- heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;
- C(O)OR²; or
- C(O)R²;

and with the proviso that unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

x is 0, 1, or 2;

- (b) B represents an optionally substituted phenyl or thienyl ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a).
- (c) D represents



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- (d) E represents a chain of n carbon atoms bearing m substituents R⁶, wherein said R⁶ groups are independent substituents, or constitute nonspiro rings in which two groups R⁶ are joined, and taken together with the chain atom(s) to which said two R⁶ group(s) are attached, and any intervening chain atoms, constitute a 5 or 6- membered ring; and wherein
- n is 2 or 3;
- m is an integer of 1 or 2;

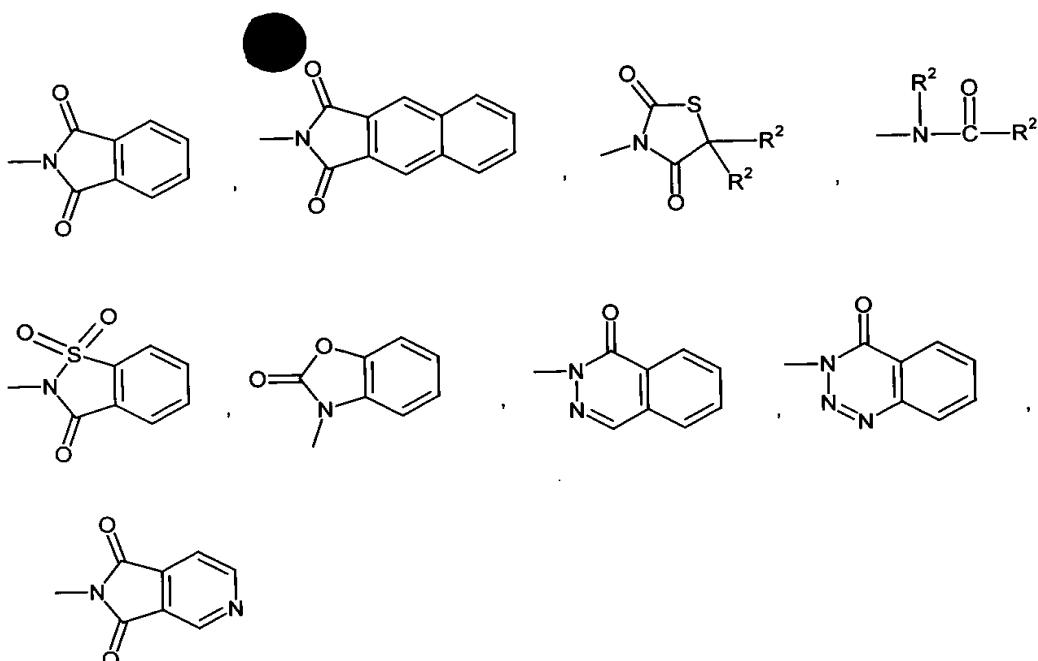
each group R⁶ is independently selected from the group consisting of:

* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

* -(CH₂)_tR⁷ wherein

t is 0 or an integer of 1 - 5; and

R⁷ is selected from the group consisting of

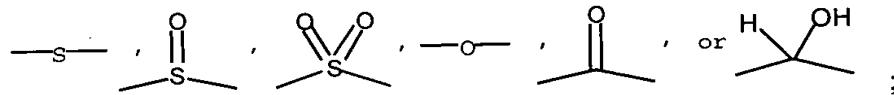


wherein

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R² is independently selected from the group consisting of: H; aryl of 6-10 carbons

- * -(CH₂)_vZR⁸ wherein
 - v is 0 or an integer of 1 to 4; and
 - Z represents



R⁸ is selected from the group consisting of:

- alkyl of 1 to 12 carbons;
- aryl of 6 to 10 carbons;
- heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
- arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

-C(O)R⁹ wherein R⁹ represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R⁸ is -C(O)R⁹, Z is S or O;
- when Z is O, R⁸ may also be -(C_qH_{2q}O)_rR⁵ wherein q, r, and R⁵ are as defined above; and

- * -(CH₂)_wSiR¹⁰₃ wherein
w is an integer of 1 to 3; and
R¹⁰ represents alkyl of 1 to 2 carbons;

and with the proviso that

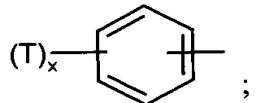
- aryl or heteroaryl portions of any of said T or R⁶ groups optionally may bear up to two substituents selected from the group consisting of OR⁴, N(R⁴)₂, -OC(R⁴)₂O-, in which both oxygen atoms are connected to the aryl ring, CON(R⁴)₂, OCOR⁴, -halogen, -NO₂, and alkyl with up to 6 carbon atoms wherein

R⁴ is defined as above;

and pharmaceutically acceptable salts and prodrugs thereof.

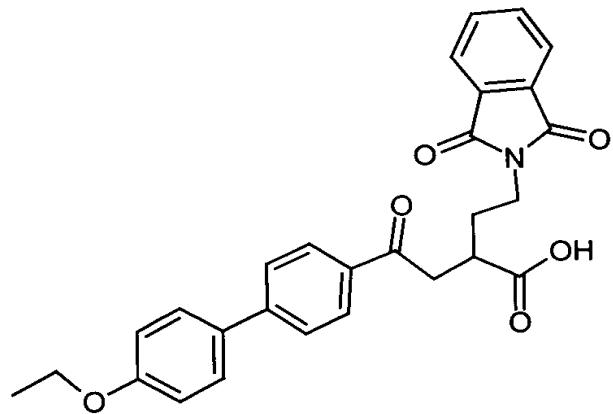
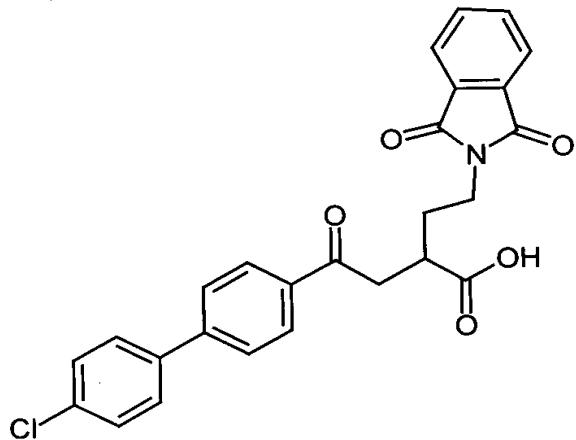
3. (Amended) The method of claim 1 or 2, wherein at least one of the units A, B, T, and R⁶ comprises a heteroaromatic ring.

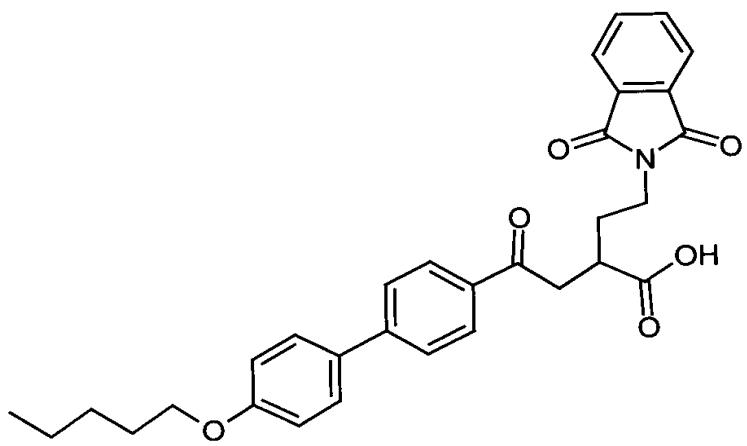
4. (Amended) The method of claim 1 or 2, wherein in said E-unit, n is 2 and m is 1.
5. (Amended) The method of claim 1 or 2, wherein A is



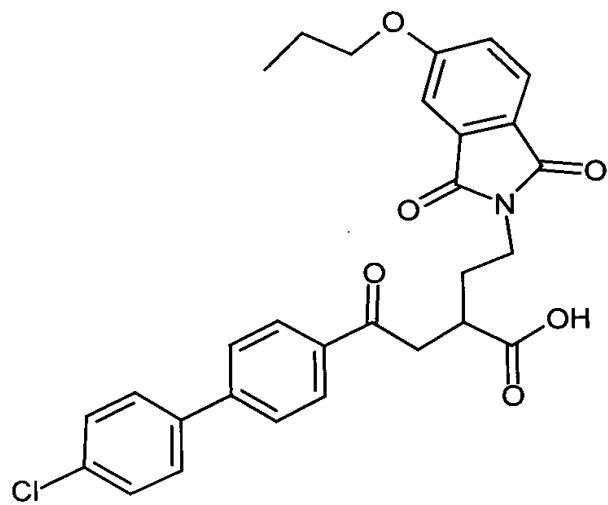
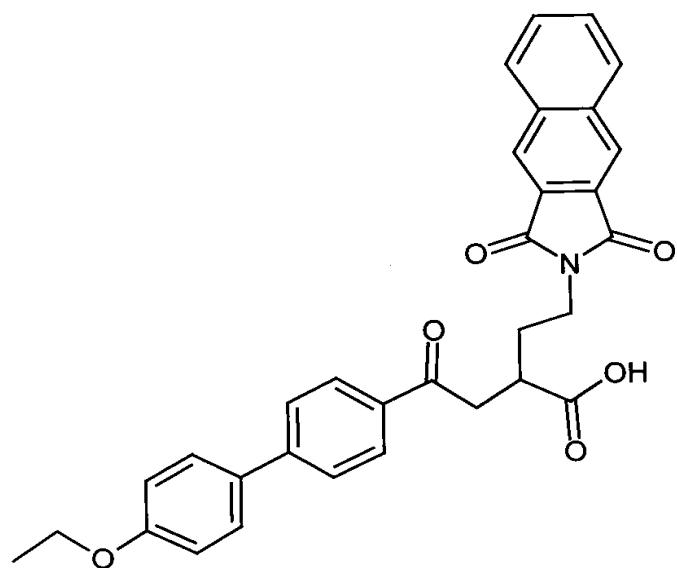
B is p-phenylene and D is a carbonyl group.

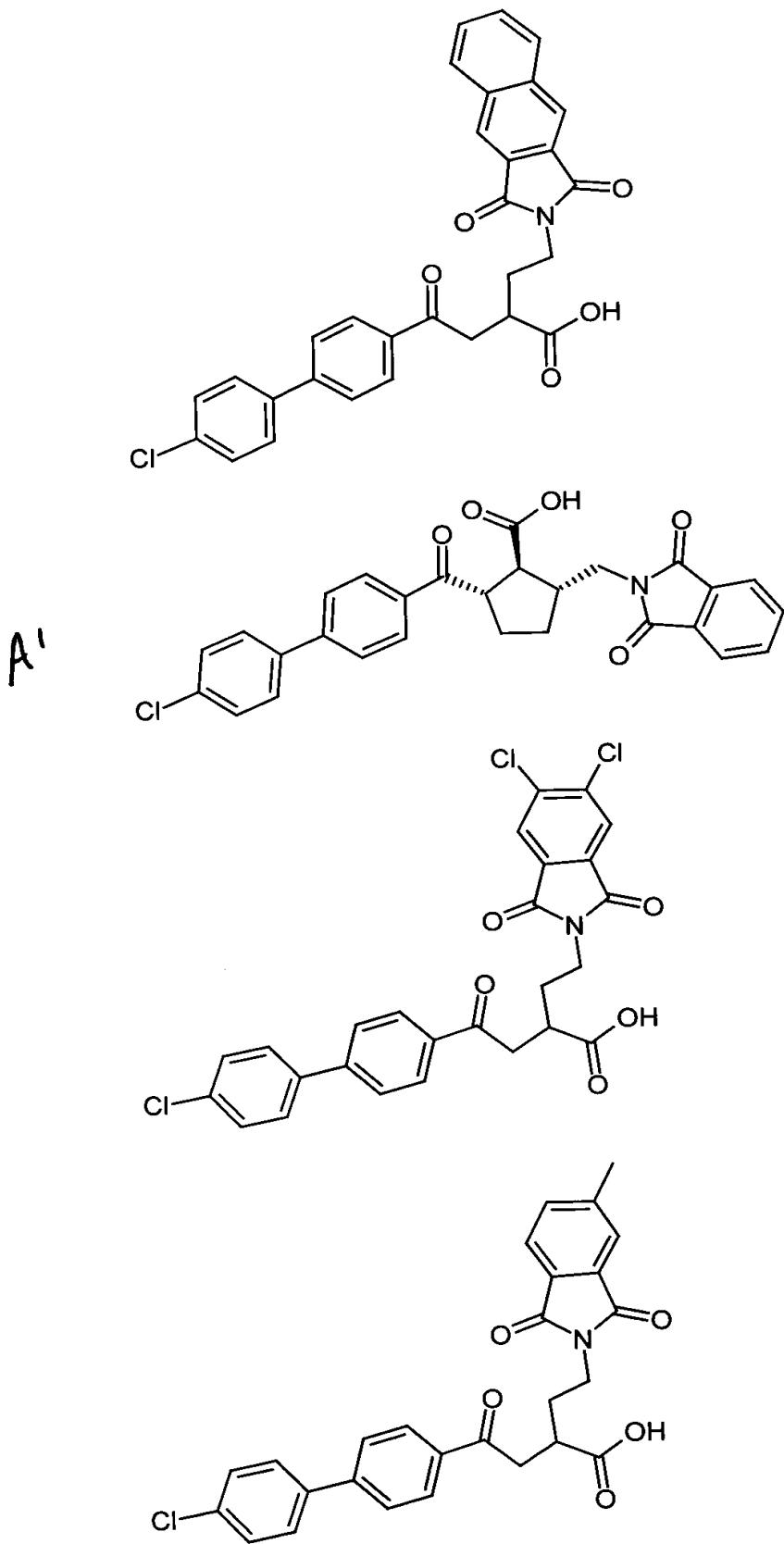
- A¹
6. (Amended) The method of claim 1 or 2, wherein the compound is selected from the following group:

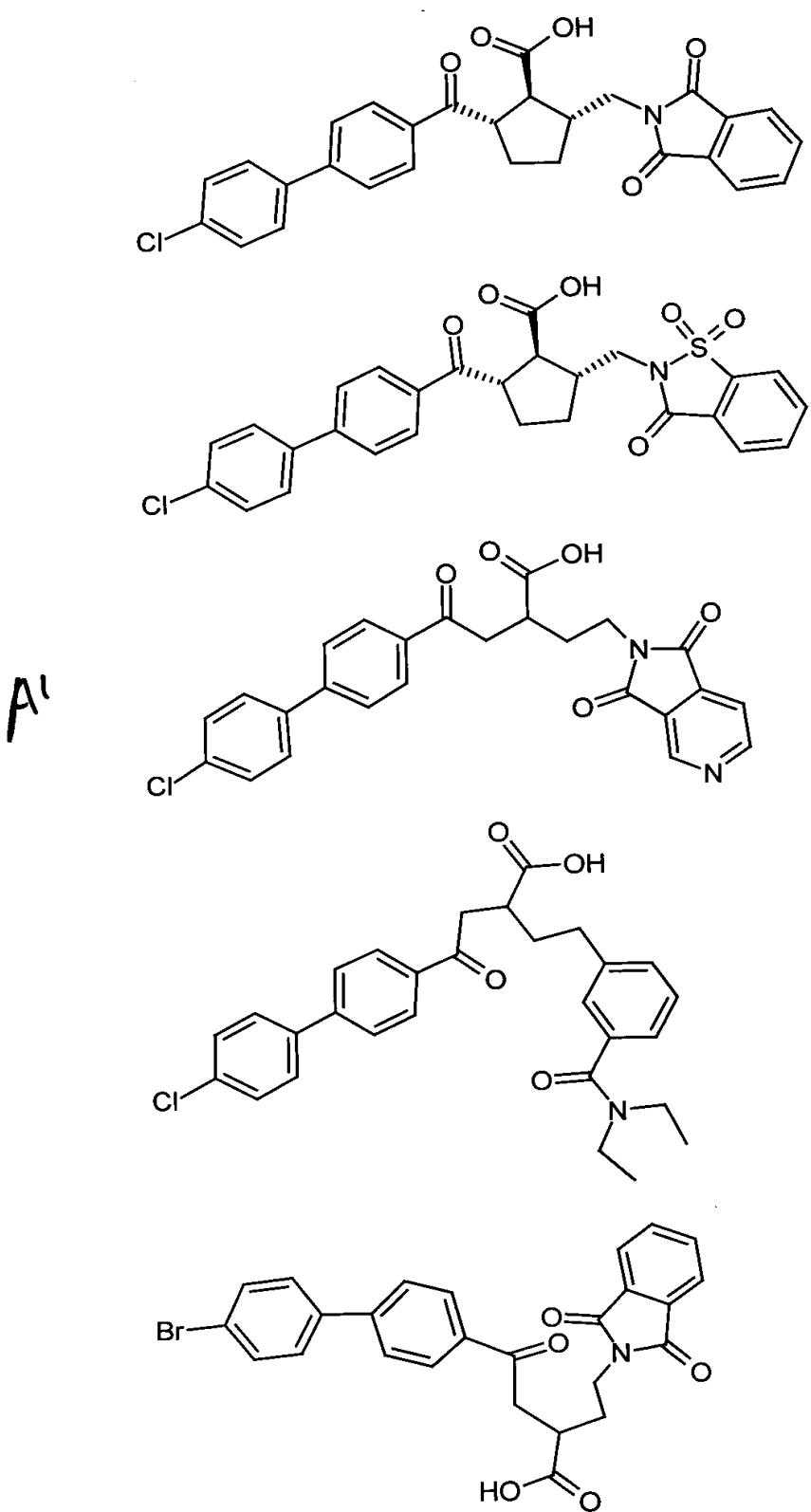


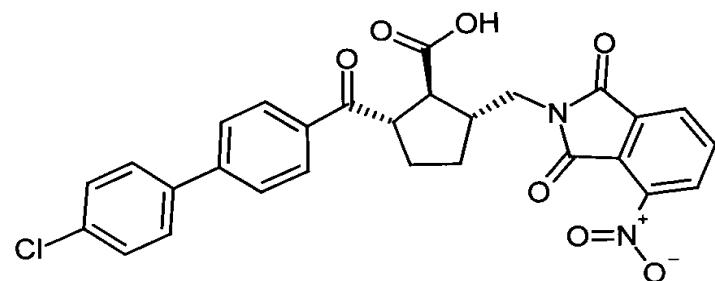
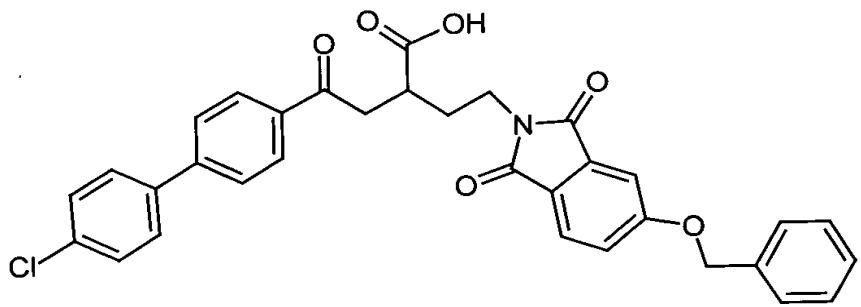


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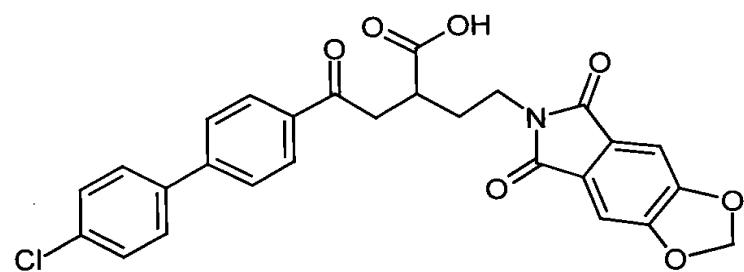
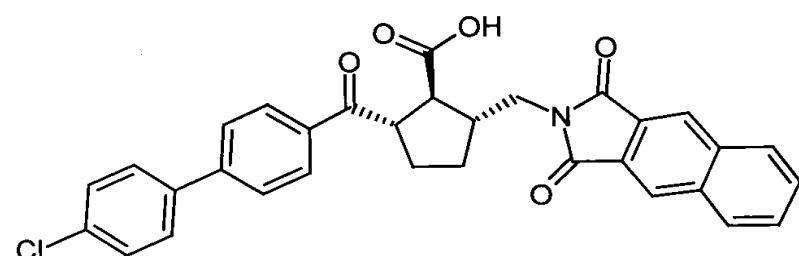
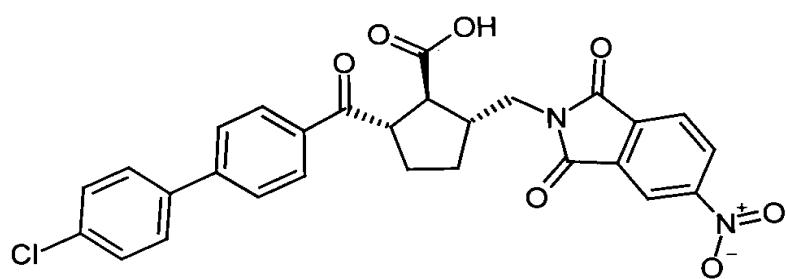


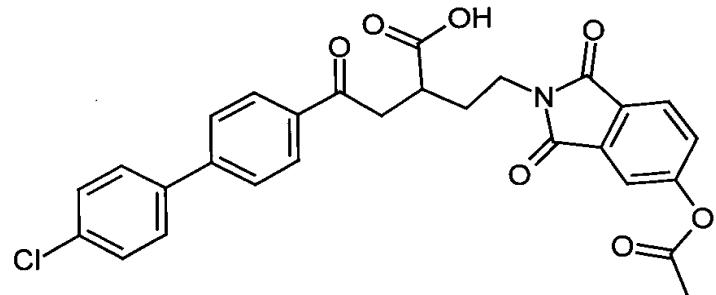
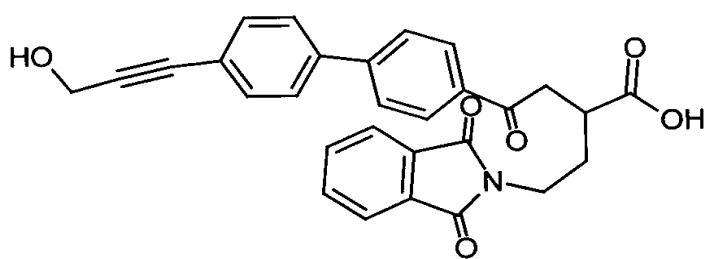
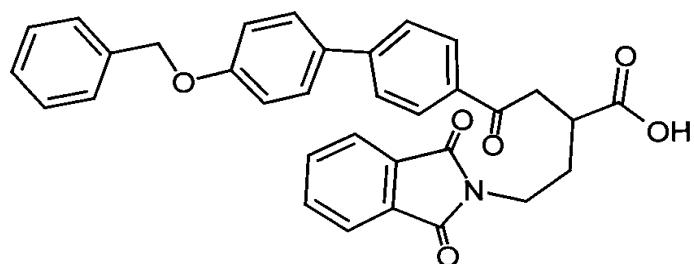
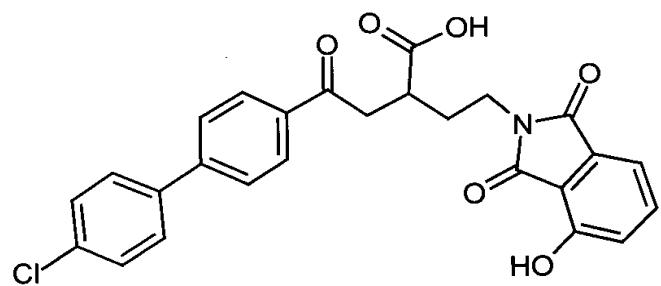
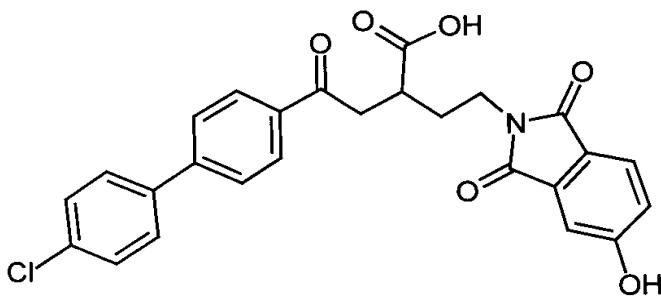






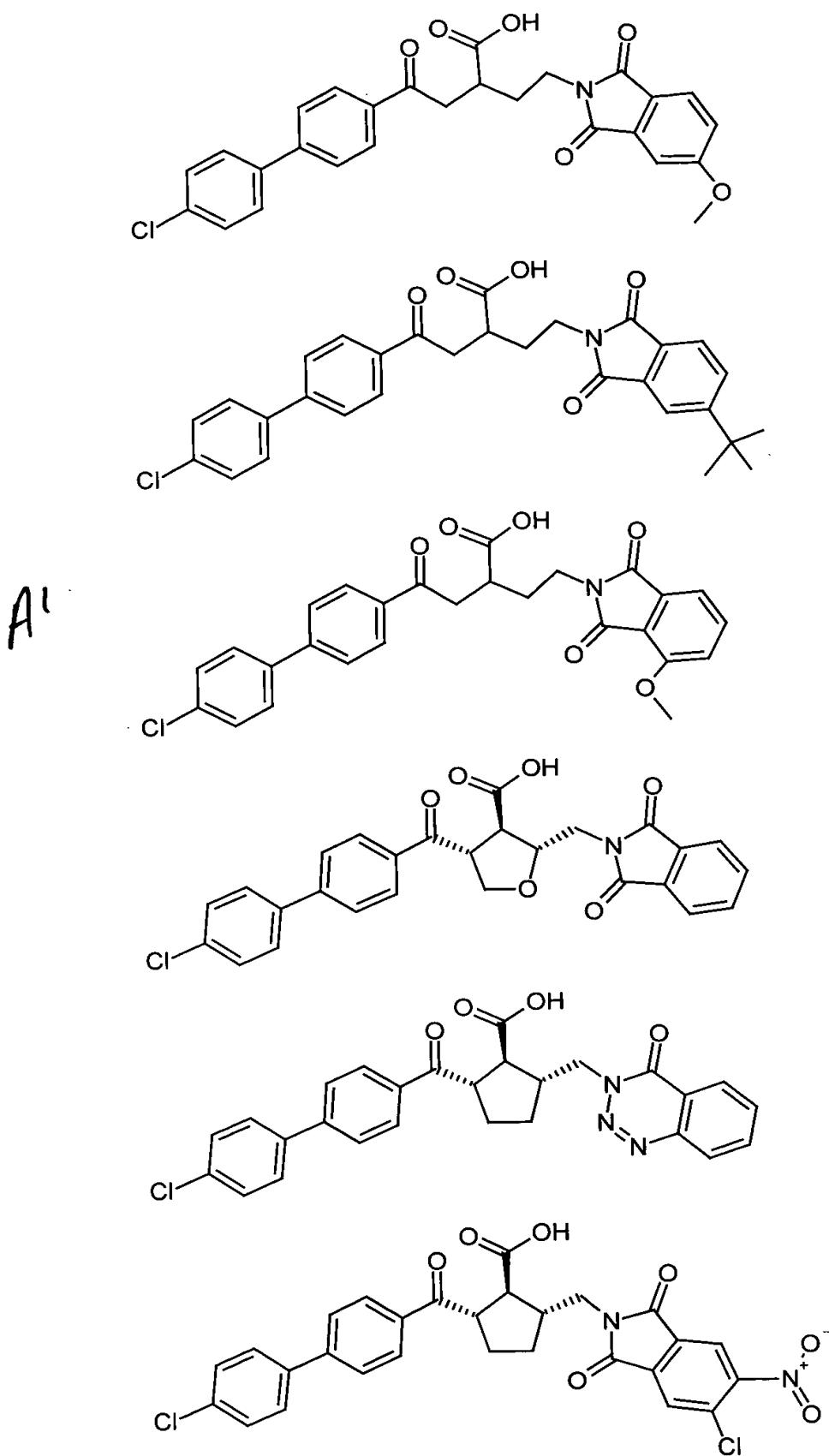
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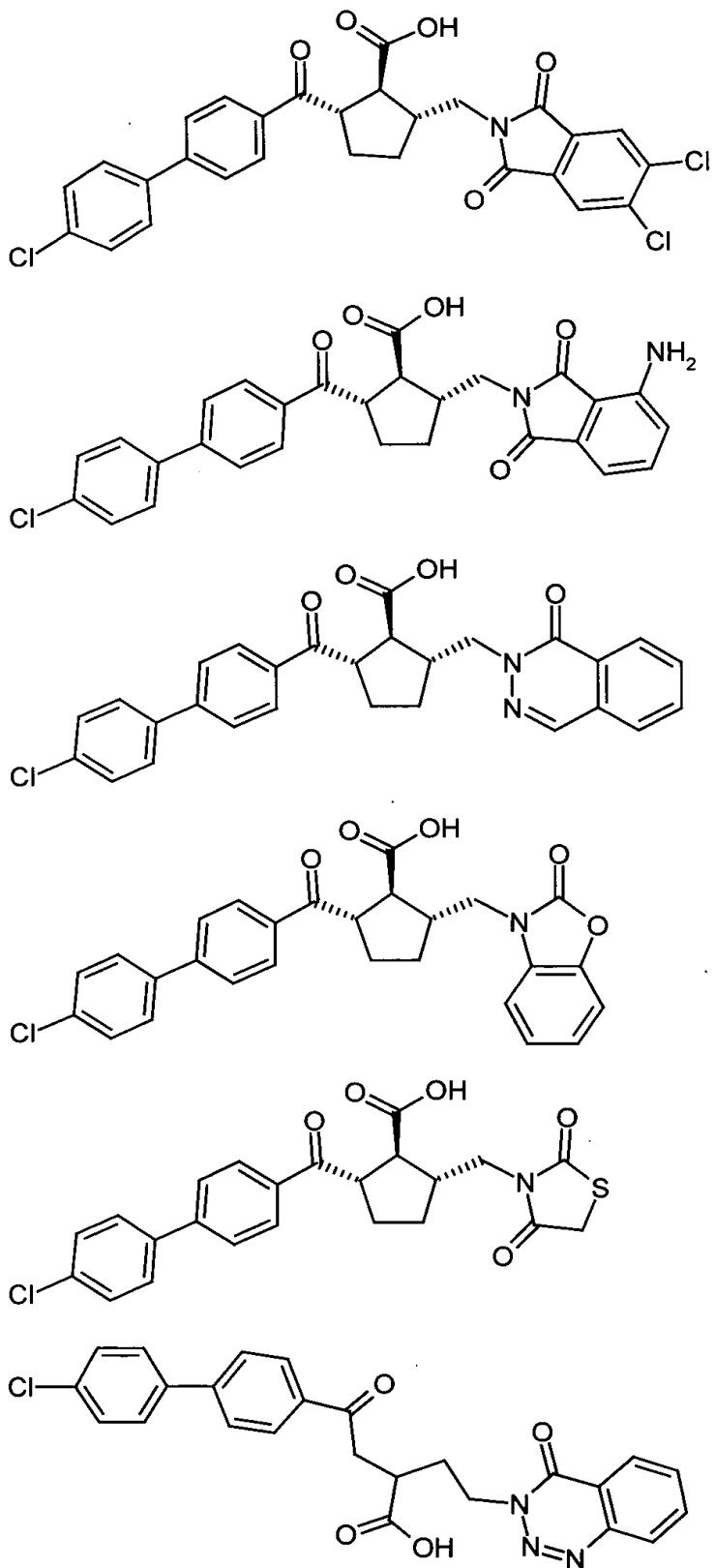


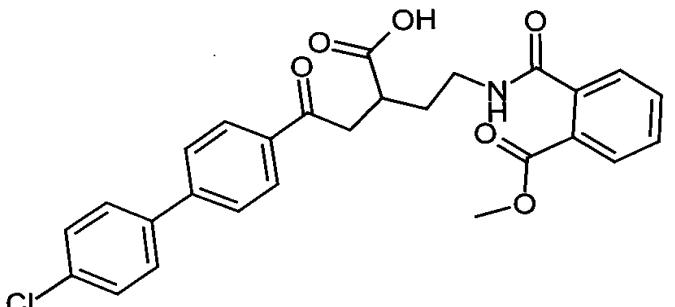


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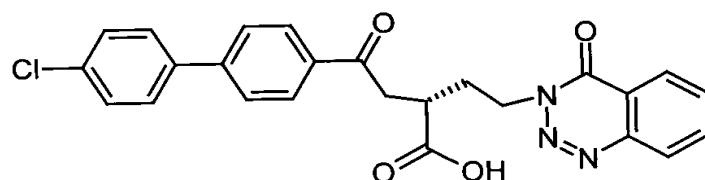
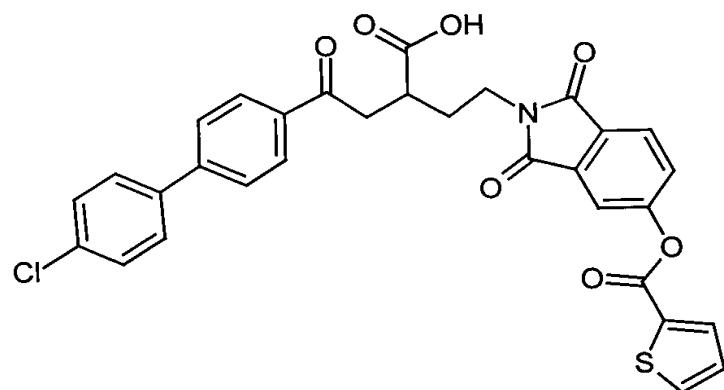
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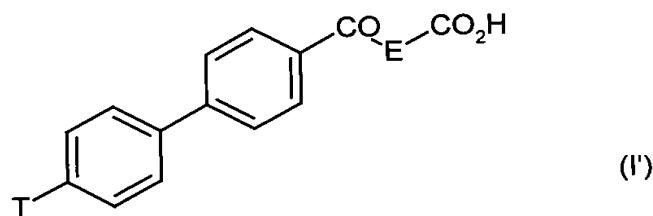
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9. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of a compound of the general formula (I')

A²

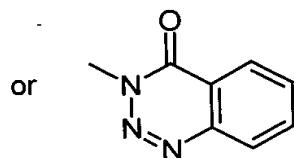
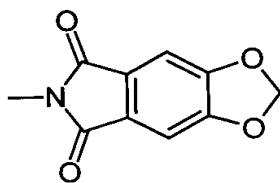
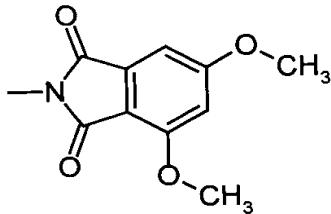
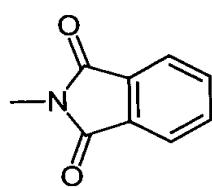


wherein

T is (C₁-C₄)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

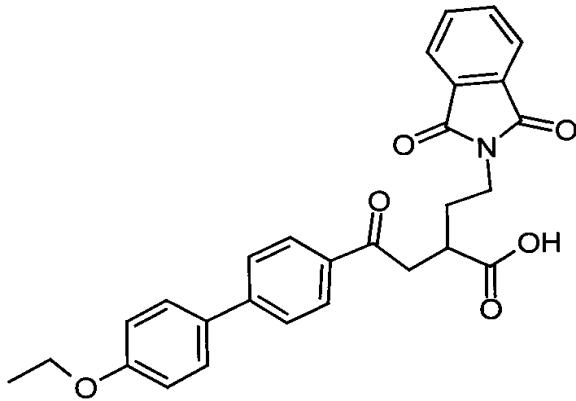
CO-E-CO₂H represents a 3-carboxyl-5-R⁷-pentan-1-on-1-yl or a 2-carboxyl-3-(R⁷-methyl)-cyclopentan-1-yl carbonyl-residue, and

R⁷ represents a group of the formula



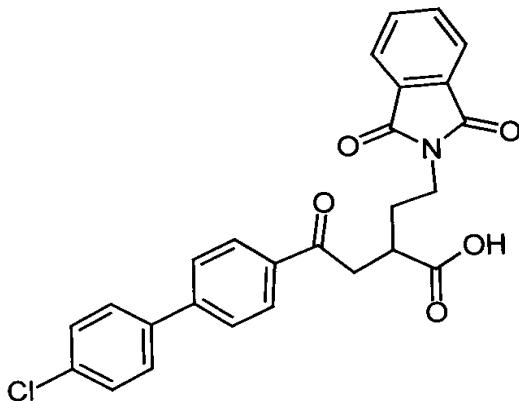
and their salts.

- A²
10. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of the compound (+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,



11. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of the compound

(+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



12. canceled.
14. The method of claim 1, 9, 10 or 11, wherein said respiratory disease is selected from the group consisting of asthma; chronic obstructive pulmonary diseases including chronic bronchitis and emphysema; cystic fibrosis; bronchiectasis; adult respiratory distress syndrome (ARDS); allergic respiratory disease including allergic rhinitis; diseases linked to TNF α production including acute pulmonary fibrotic diseases, pulmonary sarcoidosis, silicosis, coal worker's pneumoconiosis, alveolar injury in mammals, such as human, a farm animal or a domestic pet.
15. canceled.
16. (Amended) A pharmaceutical composition comprising a compound according to Claim 7 or 8 and a pharmaceutically acceptable carrier.
- A³
17. (Amended) A method of treating or preventing acute and chronic inflammatory processes, comprising administering to a mammal an effective amount of a compound according to claim 7 or 8.